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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/812,238 | 03/29/2004 | Kishore K. Wary | D6563 | 3362 |

7590 03/09/2007

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| EXAMINER | |
|---|---|
| HADDAD, MAHER M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/09/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/812,238 | WARY ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8,9,14,15 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,14,15 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/4/06 has been entered.

2. Claims 8-9, 14-5 and 32 are pending and under examination as they read on a method of inhibiting cell-cell interaction, a method of treating a patient having a pathological condition and a method of inhibiting angiogenesis and the formation of capillaries in patient with antibody directed against a peptide comprises CRGDD sequence, angiogenesis, inflammation and tumor growth as the species.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

7. Claims 8-9, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cell-cell interaction or a method of inhibiting tumor growth or angiogenesis comprising contacting the cells with an antibody directed against the sequence consisting of SEQ ID NO: 41 or the SEQ of SEQ ID NO: 2, wherein said peptide is derived from human VCIP of SEQ ID NO: 14, wherein said antibody blocks binding of $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins to VCIP, thereby inhibiting the cell-cell interaction, does not reasonably provide **enablement** for a method of inhibiting cell-cell interaction comprising contraction the cells with an antibody directed against a peptide consisting of SEQ ID NO: 41 or consisting of SEQ IN NO: 2, that is derived from a cell surface VCIP consisting of SEQ ID NO: 13, wherein said contact with the antibody blocks binding of $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins the cell surface VICP, thereby inhibiting the cell-cell interaction, in claim 8, wherein said cell-cell interaction is mediated by any "integrin ligand" in claim 9, wherein said cell-cell interaction contributes to inflammation in claims 14 and 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification does not provide sufficient enablement to inhibit any cell-cell interaction such the one that contributes to inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-

induced lung injury, inflammatory bowel disease, Crohn's disease, diabetic retinopathy, cardiovasculare diseases among others using the claimed antibodies.

One cannot extrapolate the teachings of the specification to the scope of the claims because the method claims are drawn to inhibiting any cell-cell interaction contributes to inflammation using anti-VCIP-RGD antibodies. The claims as written encompass a broad genus of inflammatory condition with an unlimited number of possibilities. Norman and Kubes (Microcirulation 12:91-98,2005) teach that many of the anti-adhesion therapy clinical trials have yielded disappointing outcomes (see abstract). Norman and Kubes teach that initial animal studies support therapeutic molecules that would intervene in the mechanisms underlying leukocyte recruitment may lead to the discovery of therapeutic molecules, but for as yet unknown reasons, many of the clinical trials have revealed negative results (see page 91, 1st, 1st ¶). Further, Norman and Kubes teach that it will be difficult to target certain organs such as liver and lung with anti-adhesion approaches. Moreover, the most difficult conditions will include systemic inflammatory situations such as sepsis and multiorgan involvement as is the case in trauma and multiple-organ failure syndrome (see Page 95, 1st col., 1st paragraph in particular). Finally Norman and Kubes teach that a magic bullet against a single-adhesion molecule will not work optimally to inhibit leukocyte recruitment (see page 95, 1st col., 2nd paragraph).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.*

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

9. Claims 8-9, 14-15 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Humtsoe et al (IDS Ref. No. c) (April 2003).

Humatsoe et al teach a method of inhibiting cell-cell interaction comprising contacting the cells with anti- VCIP-RGD antibody. Humatsoe et al teach that dose-dependent inhibition of cell aggregates in response to the anti-VCIP-RGD (claimed SEQ ID NO: 41 and 2) antibody was observed (see page 1444-1545, under VCIP promotes direct cell-cell interactions and materials and methods) Humatsoe further teach that cell-cell-interactions contribute to normal as well as unwanted cell cycle progression, vascular malformation, expansion of atherosclerosic lesion, invasion and growth of soild tumor (see page 1548, 2nd col., last ¶ in particular). Finally, Humatsoe et al teach that inhibitors of cell-cell interactions can be useful for developing novel therapeutic approaches to treat disease where these interactions have clear pathological consequences, scuh as inflammation, thrombosis, atherosclerosis, restenosis and tumor-induced angiogenesis (see page 1551, 1st col., 2nd ¶ in particular).

The reference anticipates the claimed invention.

10. Claims 8-9 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Vassilev et al (Blood. 1999 Jun 1;93(11):3624-31), as is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) for the same reasons set forth in the previous Office Actions mailed 9/30/05 and 5/31/06.

Claim 15 is included because Vassilev et al teach that RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory processes. Vassilev teaches that antibodies in IVIg that recognize the RGD adhesion motif may contribute to the anti-inflammatory effects of IVIg (see page 3629, 1st col., last ¶ in particular). Further, Vassilev teach that the MoAbs to integrins and adhesion-blocking peptides have been used in experimental models of autoimmune and inflammatory disease as well as the treatment of patients with solid organ allograft rejection (see page 3629, 2nd col. 2nd ¶ in particular).

Applicant's arguments, filed 12/4/06 and 2/22/07, have been fully considered, but have not been found convincing.

Applicant argues that claim 8 recites a method of inhibiting cell-cell interaction by contacting the cells with an antibody directed to specific peptides (SEQ ID NO: and 41). Vassilev et al teach that the antibody was directed against the 10-amino acid peptide containing the RGD motif (page 3624, 2nd col., lines 31-35).

Regarding Applicant insistence that "the IVIg were directed against the 10-amino acid peptide containing the RGD motif". It appears that Applicant mischaracterizes Vassilev reference teachings. IVIg contains the pooled IgG immunoglobulins (antibodies extracted from the plasma of over a thousand blood donors). Among the IgG immunoglobulin pool, there is approximately 0.15% that binds to RGD (see page 3629, 2nd col., end of the top ¶). However, the 10-amino acid peptide was used to obtain the 0.15% anti-RGD antibodies from the pool by affinity purification.

Applicant argues that while the peptide of Vassilev et al and those of the instant invention comprise the RGD motif sequence, the rest of the amino acids within these peptides are different. Accordingly, Applicant concludes that the peptides differ not only in the number of amino acid residues but also in the type of amino acids. The teaching in Vassilev reference of the ability of the antibody to bind fibronectin, fibrinogen, vitronection, VWF and laminin in a dose dependent manner is inconsequential. That is Vassilev et al do not teach that the antibody was also directed against the specific 5 amino acid peptide of claimed SEQ ID NO: 41 or the specific 20 amino acid peptide of claimed SEQ ID NO: 2.

However, Vassilev et al reference teaches that the anti-RGD antibodies bind to peptide and proteins expressing the RGD sequence (see page 3625, 1st col., under Binding assays). Given that the claimed SEQ ID NO: 2 and 41 peptides express the RGD sequence, the referenced anti-RGD antibodies would bind to the claimed SEQ ID NO: 2 and 41 in the absence of evidence to the contrary.

Applicant submits that since the claimed method uses an antibody directed to the "specific peptides" whether an antibody generated against these peptides would block the binding of integrins to cell surface VCIP is not inherent based on the teachings of the references cited by the Examiner.

However, given that the specific peptides (SEQ ID NOS: 2 and 41) and VCIP protein (SEQ ID NO: 13) express RGD motif sequence, the referenced anti-RGD antibodies would have the inherent property of binding VCIP of SEQ ID NO: 13 in the absence of objective evidence to the contrary.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 15 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 5,807,819 in view of U.S. Pat. No. 5,567,440 and Vassilev et al as is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886).

The `819 patent teaches a method of treating angiogenesis comprising administering to the subject RGD-containing peptides (see abstract and the entire document). The `819 patent further teaches that angiogenesis is required for the growth of solid tumors and neovascularization serves as a conduit for metastasis (see col. 9, lines 19-21 in particular). Further, the `819 patent teaches methods of using the Arg--Gly--Asp containing peptides such as CRGDDVC (patented SEQ ID NO: 17) to alter $\alpha v\beta 3$ integrin receptor-mediated binding of a cell endothelial cell to a matrix. The `819 patent teaches further teaches methods for ameliorating the severity of a pathology characterized by an undesirable level of angiogenesis in a subject using RGD-containing peptides (see the entire document including the abstract).

The claimed invention differs from the `819 patent teachings only by the recitation of antibody to SEQ ID NO: 2 or 41.

The `440 patent teaches that cell adhesion plays an important role in human disease. These interactions proceed by the interaction of receptors upon the surface of a cell with proteins or glycosaminoglycans upon the surface of another cell or within the extracellular matrix. The `440 patent further teaches that routes to the interruption of these interactions typically involve competitive inhibition of these receptor-ligand interactions, for example, with antibodies, soluble ligands which act as receptor antagonists (e.g., cyclic RGD peptides), soluble receptors, or other competitors (see col., 1 lines 17-30 in particular).

Vassilev *et al* teach a method of inhibiting platelet aggregation "cell-cell interaction" by anti-RGD antibodies (see page 3626, 1st col., 2nd paragraph and Fig. 4 in particular). Vassilev *et al* further teach that RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory processes. For instance, cyclic RGD peptides have been shown to inhibit $\alpha 4\beta 1$-dependent adhesion of T cells to cytokine-activated endothelial cells (see page 3629, 1st col., last paragraph to the 2nd col., 1st paragraph in particular). Further, antibodies "cross-react" with antigens with homolgous amino acid residues. The reference anti-RGD antibody would bind to the peptide comprises SEQ ID NO: 41 and 2 due to the shared sequence homology. As is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) who characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

The limitation "blocks the binding of integrins to cell surface VCIP" would be expected properties of the resultant method.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CRGDDVC cyclic peptide taught by the `819 patent with anti-RGD antibody taught by Vassilev *et al* in a method of inhibiting angiogenesis in a subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because routes to the interruption of cell-cell interactions typically involve competitive inhibition of these receptor-ligand interactions with either receptor antagonists (e.g., cyclic RGD peptides), antibodies or other competitors.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 12/4/06 and 2/22/07, have been fully considered, but have not been found convincing.

Applicant submits that Vassilev et al's antibodies is directed against the 10 amino acids peptide and binds fibronectin, fibrinogen, vitronectin, VWF and laminin. There is no clear teachings or suggestion in the Vassilev et al reference of the ability of the antibody to bind to "instant peptides" and in the ability of the antibody to block binding of αvβ3 and/or α5β1 integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein. Applicant concluded that the prior art references combined do not teach or suggest all claim limitations and provide no incentive to a person ordinary skill in the art.

However, Given that Vassilev et al's anti-RGD antibodies bind to peptide and to proteins expressing RGD sequence such as the RGD-containing decapeptide, fn, vitronectin, fg, and vWf, (see page 3625, 1st col., under Binding assays), the referenced anti-RGD antibodies would bind the claimed RGD-containing sequences of SEQ ID NOS: 2, 41 and 13 in the absence of evidence to the contrary. The referenced antibodies would be expected to block binding of αvβ3 and/or α5β1 integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein.

Applicant further argues that the anti-RGD antibodies taught by Vassilev et al, binds a peptide with an amino acid sequence that differs from the instant peptides in number and type.

However, both the referenced and the claimed peptides/proteins contain the RGD motif to which the reference antibodies bind, irrespective of the size and type of the peptide. Vassilev et al provide strong evidence that the anti-RGD antibodies bind multiple RGD containing proteins. Accordingly, the ordinary skilled in the art would expect the referenced antibody to bind to the claimed RGD-containing peptides and VCIP protein of SEQ ID NOS: 2, 41 and 13, in the absence of evidence to the contrary.

Applicant submits that the Examiner fails to provide any scientific evidence to support that the referenced anti-RGD antibodies binds the claimed RGD-containing peptides and protein.

Contrary to applicant submission, the Examiner would like to point to Bendayan (of record), which was used by the Examiner to provide a scientific evidence to support that the referenced antibodies would bind to the claimed sequences base on the shared RGD motif. Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular). Accordingly, the referenced anti-RGD antibodies, would bind to the claimed RGD-containing peptides and protein of SEQ ID NOS: 2, 41, and 13.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 20, 2007

Maher Haddad

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